Alerts, Notices, and Case Reports

Acute Renal Failure Complicating Nonfulminant Hepatitis A

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RENAL INVOLVEMENT IS well known in association with viral hepatitis B and C infection, but rarely recognized with hepatitis A virus (HAV). Usually identified as a mild self-limited disease lacking extrahepatic involvement, HAV has recently been shown to have the potential for causing a broad spectrum of systemic complications ranging from arthritis, vasculitis, and cryoglobulinemia to acute renal failure, fulminant hepatic failure, and death. Described here is a case of acute nonfulminant hepatitis A complicated by acute renal failure.

Report of a Case

The patient, a previously healthy 35-year-old woman with a history of only seasonal asthma, was seen after one week of nausea, vomiting, and malaise. She was found to have mild icterus with a serum alanine aminotransferase level of greater than 4,000 U per liter, a γ-glutamyltransferase level of 463 U per liter, and a total bilirubin value of 50 μmol per liter (2.9 mg per dl). Urinalysis showed 2+ proteinuria with 2 to 3 erythrocytes per high-power field, but was otherwise normal. Serum creatinine and other laboratory values were normal, and the results of the physical examination were otherwise unremarkable. An acute hepatitis panel revealed positive anti-HAV immunoglobulin (Ig) M antibodies. The patient was treated symptomatically and discharged without hospitalization.

The patient presented a week later with worsening jaundice, malaise, fatigue, dark urine, and light-colored stools and was admitted to the hospital for further evaluation. She said she did not have fever, chills, or other notable symptoms. She was married and monogamous, with no history of injection-drug use, alcohol abuse, or smoking, and taught at a local elementary school. She reported taking an over-the-counter ibuprofen tablet about two weeks before this admission, but was using no other medications.

On admission, the patient's temperature was 36.7°C (98.1°F), her pulse rate was 67 beats per minute, and her blood pressure was 138/80 mm of mercury without any orthostatic changes. On physical examination, she had jaundice and mild hepatomegaly; there were no stigmata of chronic liver disease or peripheral edema.

Laboratory studies were remarkable for improving liver function test values and a serum creatinine level of 710 μmol per liter (8.0 mg per dl). Viral serologic tests again showed the presence of anti–HAV IgM antibodies and the absence of anti–hepatitis B core IgM antibodies, hepatitis B surface antigen, and antibodies to hepatitis C and D viruses. Tests for antinuclear antibodies were negative, and plasma complement levels were within normal limits. A urinalysis revealed 1 to 4 leukocytes and rare nonglomerular erythrocytes with few coarse granular casts. Urinary chemistry tests elicited the following values: sodium, 34 mmol per liter; chloride, 44 mmol per liter; creatinine, 5,142.7 mmol per liter (58 mg per dl); and a calculated renal failure index of 4.7. Urine culture and Hansel staining were negative for urine eosinophils. A renal sonogram showed normal kidneys with no signs of obstruction.

Despite volume expansion, the patient's serum creatinine level increased to 730 μmol per liter (8.2 mg per dl) on hospital day 2. A subsequent renal biopsy showed mild glomerular mesangial hypercellularity, interstitial edema with a pronounced mononuclear cell infiltrate, and occasional eosinophils (Figure 1). Immunofluorescent staining of the biopsy specimen showed mesangial staining for IgA, IgM, IgG, and C1q. The patient's renal function improved spontaneously over the next several days with conservative measures, and she did not require dialysis. At the time of discharge, she was asymptomatic with improving renal and liver function indices. At one-year follow-up, she was well and asymptomatic with normal liver and renal function.

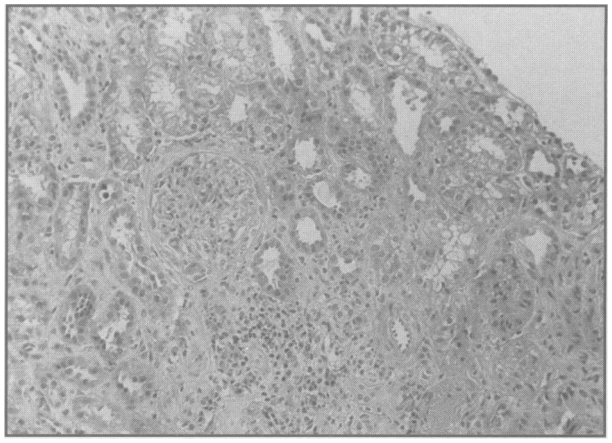

Figure 1.—A photomicrograph of a renal biopsy shows mild mesangial hypercellularity and interstitial edema with mononuclear cell infiltrate and occasional eosinophils (hematoxyn and eosin stain, original magnification ×100).

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ABBREVIATIONS USED IN TEXT

HAV = hepatitis A virus
Ig = immunoglobulin

Discussion

Hepatitis B and C have well-described renal involvement that can lead to acute renal failure, and the mechanism is thought to be associated with immune complex deposition.[1-3] Although a few mechanisms have been postulated, the exact process behind hepatitis A-induced acute renal failure remains to be elucidated. A review of the 32 reported cases of acute renal failure associated with HAV in the world literature,[2-28] along with the current case (Table 1), yielded 17 cases with a documented renal biopsy. Of these 17 cases, 5 revealed immunologic involvement as reflected by immune complex deposition. The other 12 cases showed either interstitial nephritis or acute tubular necrosis. Although the onset from a viral prodrome to acute renal failure was not recorded in all cases, it is a fair generalization to say that it usually occurs early in the course of the illness (the average onset of acute renal failure is 10 days after the appearance of jaundice).[2-28]

Treatment in most cases required dialysis. Four patients were treated with plasmapheresis, and nine patients were treated conservatively. Rapid and complete resolution was the general rule in all cases, with only three patients having a fatal course.[2,3,25] It is notable that the three patients who died all showed renal disease consistent with acute tubular necrosis without evidence of an immunologic process.[2,3,25] All three of these patients were managed with hemodialysis; two died of sepsis,[2,25] and the other had a fatal myocardial infarction.[3] The age variation

TABLE 1.—*Reports of Cases of Acute Nonfulminant Hepatitis A Complicated by Acute Renal Failure**

Reference	Age, yr	Sex	Renal Biopsy Findings	Treatment	Outcome
Wilkinson et al, 1978[2]	34	F	NA	Dialysis	Resolved
Wilkinson et al, 1978[2]	49	M	Acute tubular necrosis	Dialysis	Death
Wilkinson et al, 1978[2]	35	F	NA	Dialysis	Resolved
Mizuiri et al, 1985[3]	34	M	Acute tubular necrosis	Dialysis and plasmapheresis	Death
Suga et al, 1984[7]	21	F	NA	Plasmapheresis alone	Resolved
Garel et al, 1986[8]	8	F	Mesangial proliferation	Conservative	Resolved
Garel et al, 1986[8]	10	F	Acute tubular necrosis, mesangial proliferation, interstitial nephritis	Conservative	Resolved
Kramer et al, 1986[9]	30	M	NA	Dialysis	Resolved
Watanabe et al, 1986[10]	43	F	NA	Dialysis and plasmapheresis	Resolved
Eng and Chopra, 1990[13]	43	M	Lymphocytic infiltrate, focal tubular atrophy	Conservative	Resolved
Imatake et al, 1990[14]	39	F	Acute tubular necrosis, immune complex deposition†	Conservative	Resolved
Schmidli and Lynn, 1990[15]	51	M	NA	Dialysis	Resolved
Mattoo et al, 1991[17]	7	M	NA	Dialysis	Resolved
Chio and Bakir, 1992[18]	21	M	NA	Dialysis	Resolved
Geltner et al, 1992[19]	52	M	Interstitial nephritis	Dialysis	Resolved
Ilan and Galun, 1992[20]	28	M	NA	Conservative	Resolved
Konishi et al, 1993[21]	42	F	Acute tubular necrosis	Dialysis	Resolved
Phillips et al, 1993[22]	42	M	Normal	Dialysis	Resolved
Corpechot et al, 1994[23]	38	M	NA	Plasmapheresis alone	Resolved
Malbrain et al, 1994[24]	16	F	NA	Dialysis	Resolved
Malbrain et al, 1994[24]	41	F	NA	Conservative	Resolved
Malbrain et al, 1994[24]	30	M	Interstitial nephritis	Dialysis	Resolved
Ogawa et al, 1994[25]	59	M	Degenerative tubular epithelium	Dialysis	Death
Takeshita et al, 1994[26]	42	M	Mesangial proliferation, interstitial nephritis, immune complex deposition†	Dialysis	Resolved
Zikos et al, 1995[27]	33	M	Mesangial proliferation, immune complex deposition†	Conservative	Resolved
Faust and Pimstone, 1996[28]	37	F	Acute tubular necrosis	Conservative	Resolved
This case	35	F	Mesangial proliferation, immune complex deposition†	Conservative	Resolved

NA = not available

*Information from 6 references—Okushin, 1981[4]; Tanikawa, 1981[5]; Kawai et al, 1983[6]; Heldenberg and Weizer, 1989[11]; Blum and Ben-Yehuda, 1990[12]; and Tsuru et al, 1990[16]—is not included because only English-language summaries of these articles, most of which are in a foreign language, were available.

†Documented by immunofluorescence staining.

was wide, and no generalizations or trends can be deduced with regard to renal biopsy, treatment, or outcome.

From these case reports, five mechanisms of HAV-induced renal failure have been proposed. First, prerenal azotemia due to hypovolemia caused by nausea, vomiting, diarrhea, and anorexia may cause a disturbance of the renal circulation with the subsequent development of acute tubular necrosis and acute renal failure.[21] Second, immune complex deposition of various types—IgG, IgA, IgM, C3, and C1q—has been documented in five cases, including the current case, and postulated in many others.[11,14,26,27] In cases confirmed by a renal biopsy,[11,14,26,27] immune complexes are accompanied by mesangial hypercellularity with varying degrees of glomerular involvement; there was no tubular immunologic involvement. Moreover, viral particle deposition has been identified in kidney specimens obtained from animals infected experimentally with HAV.[29] Third, endotoxin may be present in the circulation of patients with substantial liver impairment, even in the absence of true infection.[30,31] Endotoxin may induce renal vasoconstriction with possible deposition of fibrin and increased sympathetic tone, which may lead to acute tubular necrosis and acute renal failure. Fourth, hyperbilirubinemia may cause vasoconstriction of the renal vasculature, leading to renal failure.[32] Fifth, a direct cytopathic effect by HAV has also been proposed as a cause of acute renal failure.[6] Furthermore, it should be noted that all of the aforementioned factors may contribute to a multifactorial cause of HAV-induced renal failure.

In our evaluation of the current case of HAV-induced renal failure, we speculate that each of the aforementioned mechanisms, with the possible exception of prerenal azotemia, might have contributed to the development of transient renal failure in our patient. It is unlikely that her ibuprofen use caused the episode because of the negligible amount of ibuprofen taken and the urine Hansel stain negative for eosinophils, which are generally present in cases of drug-induced acute renal failure. Our review of this case and the relevant literature suggests that there is strong evidence to implicate HAV as a cause of—and not only an association with—acute renal failure. It remains to be elucidated why the histopathologic features are so variable in these cases of HAV-induced acute renal failure and which factors predispose a patient to have immunologic involvement versus interstitial and tubular involvement.

Finally, physicians must be aware of the spectrum of systemic involvement associated with hepatitis A, including the possibility of acute renal failure.

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